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Nafamostat Mesilate

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Key Words: Acute pancreatitis—Cerebral vasospasm—Disseminated intravascular coagulation—Extracorporeal circulation—Nafamostat mesilate—Synthetic protease inhibitor.

INTRODUCTION

Nafamostat mesilate (6-amino-2-naphthyl p-guanidinobenzoate dimethanesulfonate, FUT-175) (NM) is a synthetic protease inhibitor that was prepared by Fujii et al. (19). Its structure appears in Fig. 1. This compound inhibits various serine proteases generated during the coagulation cascade and the inflammatory process. Because of these inhibitory properties, NM is being used in Japan for treating patients with disseminated intravascular coagulation (DIC) and acute pancreatitis (50,59).

This chapter will describe the pharmacological actions of NM and the possible mechanisms underlying its efficacy in treating disseminated intravascular coagulation. Its use in treating such conditions as acute pancreatitis, plasmapheresis, hemodialysis (extracorporeal circulation), and cerebral vasospasm are described.

SYNTHESIS

As seen in Fig. 1. NM is prepared by the condensation of 4-guanidinobenzoic acid (I) with 6-amino-2-naphthol (II) in pyridine either by means of DCC or the acid chloride of the compound I (III), at room temperature (19). The NM thus synthesized is colorless and odorless. Its melting point is 260°C (decomp.).

PHARMACOLOGY

Effect on Coagulation and Fibrinolysis

The inhibitory effects of NM on proteases of the coagulation and fibrinolysis systems are summarized in Table 1. Serine proteases comprise most of those generated during coagulation and fibrinolysis. As shown in Fig. 2, NM inhibits activated factor (F) VII (F.VIIa), F.Xa, thrombin, F.XIIa, kallikrein, plasminogen activators, and plasmin. NM

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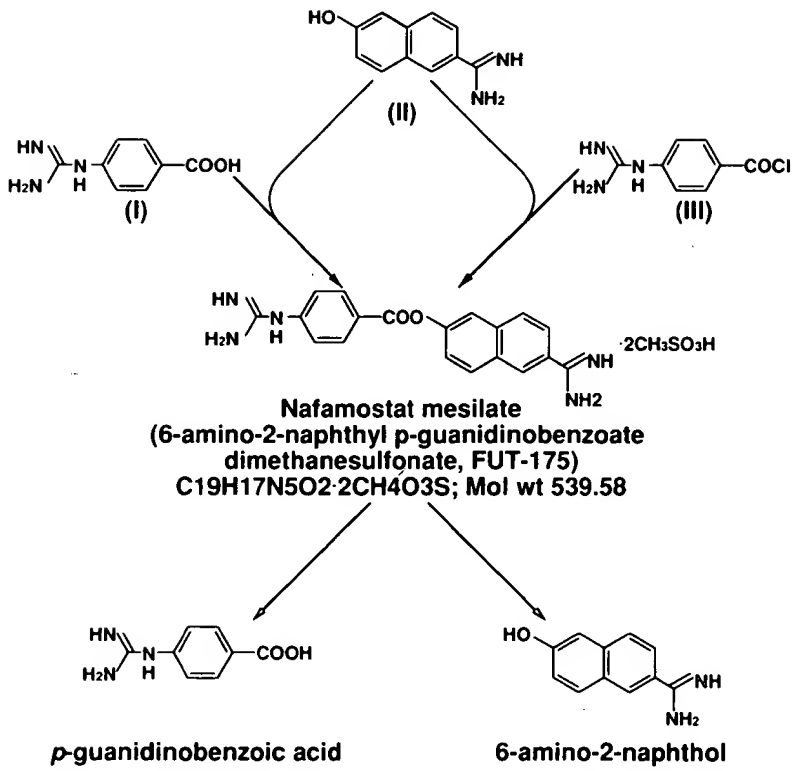

FIG. 1. Chemical structure of nafamostat mesilate, its synthesis and metabolism.

inhibits thrombin and F.Xa in competitive fashion with inhibition constant (Ki) values in the order of 10^{-7}–10^{-6} *M* (19,26,51) and 10^{-6}–10^{-4} *M* (26,51), respectively. NM was recently shown to inhibit F.VIIa, the enzyme that initiates the extrinsic pathway of coagulation by complexing with tissue factor (TF) in a competitive fashion with a Ki of 2.4×10^{-7} *M* (67). The inhibition of F.VIIa has not been demonstrated with such synthetic protease inhibitors as gabexate mesilate or argatroban, both of which are being used in Japan for treating DIC (67). NM inhibits the TF-F.VIIa complex to the same extent as F.VIIa in a competitive fashion with a Ki of 2.0×10^{-7} *M* (68).

NM inhibits the coagulation enzymes involved in the intrinsic pathway of coagulation such as F.XIIa and kallikrein in a competitive fashion with Ki values of 1.05×10^{-7} *M* and 1.2×10^{-8} *M* (51), respectively. Consistent with these observations, NM dose-dependently prolongs the prothrombin time and the activated partial thromboplastin time (26).

The effects of NM on the various serine proteases involved in fibrinolysis have been studied. NM inhibits tissue type- and urokinase type-plasminogen activators, the enzymes that activate plasminogen to plasmin, with Ki values of 1.08×10^{-6} *M* and 1.92×10^{-8} *M*, respectively (51). Plasmin, an enzyme responsible for degradation of fibrin, is also competitively inhibited by NM with Ki values of 3.74×10^{-6} *M* (51) or 3.0×10^{-8} *M* (4).

TABLE 1. *Effects of nafamostat mesilate on serine proteases*

Protease	Ki (*M*)	Substrate	Reference
Thrombin			
α-Thrombin	1.3×10^{-6}	S-2238	(26)
	5.8×10^{-7}	TAME	(4)
	8.4×10^{-7}	TAME	(19)
	4.8×10^{-6}	BCP100	(51)
β-Thrombin	9.0×10^{-6}	BCP100	(51)
γ-Thrombin	1.1×10^{-6}	BCP100	(51)
Factor VIIa	2.4×10^{-7}	S-2288	(67)
Tissue factor-Factor VIIa	2.0×10^{-7}	S-2288	(67,68)
Factor Xa	4.1×10^{-6}	S-2222	(26)
	1.2×10^{-4}	S-2222	(51)
Factor XIIa	1.1×10^{-7}	S-2302	(51)
Plasma kallikrein	1.2×10^{-8}	S-2302	(51)
Activated protein C	1.1×10^{-7}	S-2366	(51)
Plasmin	3.0×10^{-8}	TAME	(4)
	3.7×10^{-6}	S-2251	(51)
t-PA	1.1×10^{-6}	S-2444	(51)
Urokinase	1.9×10^{-8}	S-2444	(51)
C1r	4.4×10^{-7}	AAME	(4)
	1.4×10^{-8}	AAME	(19)
C1s	3.5×10^{-8}	AGLME	(4)
	3.8×10^{-8}	ATEE	(19)
B	6.0×10^{-5}	Leu-Ala-Arg-NE	(29)
Cobra venom factor · Bb	4.0×10^{-5}	Leu-Ala-Arg-NE	(29)
Trypsin	1.6×10^{-8}	S-2222	(51)
	1.2×10^{-8}	TAME	(4)
	1.5×10^{-8}	TAME	(19)
Pancreatic kallikrein	3.2×10^{-7}	TAME	(4)

TAME: tosyl-L-arginine methyl ester
AGLME: acetylglycyl-L-lysine methyl ester
AAME: acetyl-L-arginine methyl ester
ATEE: acetyl-L-tyrosine ethyl ester
BCP100: Phe-Pro-Arg-amino-nitro-benzoic acid-isopropylamide
S-2238: H-D-Phe-Pip-Arg-p-nitroanilide · 2HCl
S-2288: H-D-Ile-Pro-Arg-p-nitroanilide · 2HCl
S-2222: Bz-Ile-Glu-(γ-OR)-Gly-Arg-p-nitroanilide · HCl (R = H; 50%, R = CH; 50%)
S-2302: H-D-Pro-Phe-Arg-p-nitroanilide · 2HCl
S-2366: <Glu-Pro-Arg-p-nitroanilide · HCl
S-2251: H-D-Val-Leu-Lys-p-nitroanilide · 2HCl
S-2444: <Glu-Gly-Arg-p-nitroanilide · HCl

Effect on Complement System

NM inhibits C1r in a competitive fashion with a K_i of 1.4×10^{-8} *M* and C1s with a K_i of 3.5×10^{-8} *M* (19) in the classical pathway. NM has not been shown to inhibit C2 (21). In the alternative pathway, B and D are noncompetitively inhibited by NM with a K_i value of 6.0×10^{-5} *M* (29) and IC_{50} of 1.4×10^{-4} *M* (19), respectively (Fig. 2). The complement-mediated hemolysis produced *in vitro* by activation of both the classical and alternative pathway is inhibited by NM with an IC_{50} in the order of 10^{-8}–10^{-7} *M* (19).

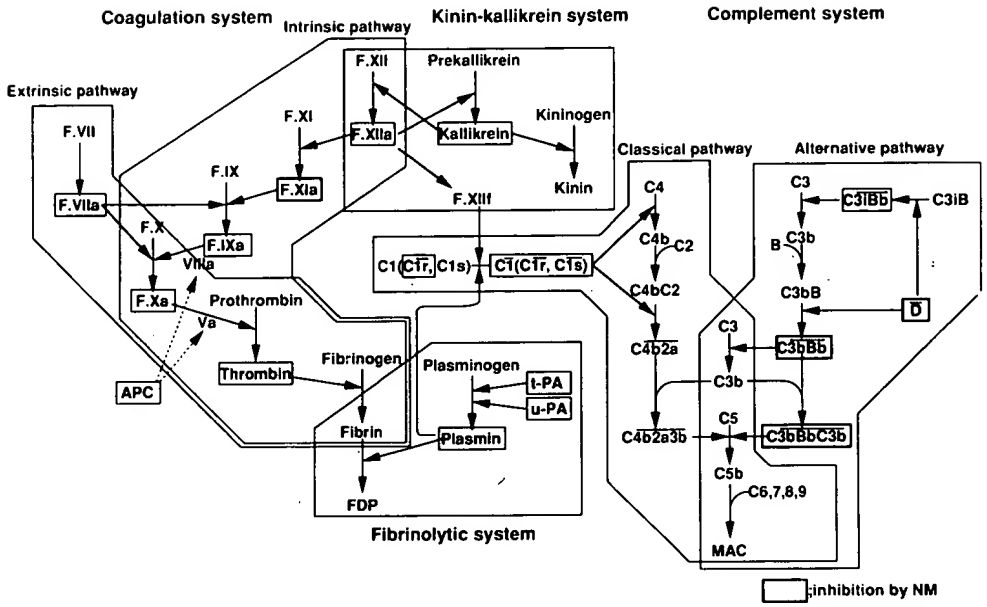

FIG. 2. Effects of nafamostat mesilate on various proteases in coagulation, fibrinolysis, and complement systems.

Effect on Other Proteases

Among the granulocyte proteases, NM inhibits cathepsin G with IC_{50} of 7.1×10^{-4} *M* (20). It inhibits trypsin in a competitive fashion with a Ki of 1.5×10^{-8} *M* (4), while it only slightly inhibits chymotrypsin (IC_{50}, 5.0×10^{-4} *M*) (20). Pancreatic and granulocyte elastases are not inhibited by NM (20).

Effect on Leukocytes and Platelets

NM (0.1 m*M*) inhibits the aggregation of leukocytes induced by formyl methionyl leucyl phenylalanine (fMLP) by about 60% (unpublished observation). Although it does not inhibit the fMLP-induced degranulation of leukocytes, that dose of NM inhibits the production of O_2^- induced by opsonized zymosan by about 40% (unpublished observation). NM (1 μM) inhibited the release of tumor necrosis factor-α (TNFα) from endotoxin-stimulated monocytes by about 20% (unpublished observation). Tamura et al. (65) also demonstrated that NM (0.25 m*M*) inhibits the production of O_2^-, H_2O_2, and OH by human leukocytes by about 60, 20, and 40%, respectively.

NM inhibits the platelet aggregation induced by thrombin, ADP, epinephrine, collagen (IC_{50}, 10^{-6}–10^{-5} *M*) and endotoxin (34).

PHARMACOKINETICS

With administration by intravenous drip to rabbits infusion of NM (50 μg/kg/min) resulted in plasma levels ranging from 600 to 800 ng/ml and a biological half life of 8 min (5). Plasma levels in dogs ranged from 1500 to 2100 ng/ml with a half life of 1 min (5).

Approximately 82% of the intravenously administered dose of NM was excreted in the feces of dogs (64). By intravenous administration to dogs radiolabeled NM (1 mg/kg) led to excretion of 64.6 and 17.1% of the administered dose in urine and feces, respectively, during 48 hr of administration (42). Analysis of metabolites of NM in urine and feces by thin layer chromatography showed no unmetabolized NM. p-Guanidinobenzoate (PGBA) and aminodinaphthol (AN) were the two major metabolites identified in urine and feces of dogs (60,61). About 95% of the intravenous dose was excreted in the urine of rats, while only about 10% of the dose was excreted in the bile within 48 hr of administration (64).

Plasma levels of NM in healthy volunteers following the administration of 10, 20, and 40 mg by a single intravenous drip infusion for 90 min were 10–20, 30–60, and 70–90 ng/ml, respectively (5). Plasma levels obtained in a study of multiple doses of 10 and 20 mg administered daily for 90 min for 3 days resembled those observed in the single-dose study (5). No laboratory test abnormalities were observed. Following intravenous drip infusions of 20 or 40 mg of NM administered to healthy adult men, the rate of the cumulative urinary excretion of AN, a major metabolite, was 27.1 and 30.2% of the administered dose, respectively, during 24 hr of administration (11).

TOXICOLOGY

Results of studies of the acute and chronic toxicity studies of NM in several animal species are summarized in Table 2 together with reference numbers. LD_{50} values in mice and rats were estimated from 14-day data after the administration of a single acute dose (Table 2). Acute toxic effects of NM were classified as neurological abnormalities and other. A decrease in locomotor activity, prone position, convulsions, salivation, and irregular respiration constituted the neurological signs, while intraperitoneal inflammation and pleural inflammation were the other, local toxic effects.

The chronic toxicity of NM administered intraperitoneally (i.p.) to rats, at doses ranging from 2.2 to 60.0 mg/kg for 35 days demonstrated that writhing occurred following i.p. doses that exceeded 6.6 mg/kg (Table 2). Emaciation occurred at a dose of 20 mg/kg. By intravenous administration to dogs at doses above 0.5 mg/kg for 30 days NM caused salivation or vomiting (Table 2). No abnormalities were observed in urine or blood. Vomiting, salivation or licking, defecation, urination, restlessness, prone position, and a decrease in appetite followed by weight loss resulted following the intravenous administration of NM in doses higher than 1.25 mg/kg in dogs for 180 days (Table 2).

PATHOPHYSIOLOGY OF DISSEMINATED INTRAVASCULAR COAGULATION

Disseminated intravascular coagulation (DIC) is a potentially lethal disorder in which microthrombi form in the systemic microvasculature (41). Such patients exhibit a bleeding tendency resulting from the consumption of platelet and coagulation factors and organ dysfunction produced by microcirculatory disturbances induced by plugging of the microvessels with fibrin leading to ischemia (Fig. 3). Since the extrinsic pathway of coagulation is more important than the intrinsic pathway in fibrin formation (12), tissue factor (TF), which is capable of triggering the extrinsic pathway by activation of factor VII

TABLE 2. *Toxicity studies*

Species	Reference	LD_{50} and route of NM
Acute toxicity		
Mouse	56	24.4 mg/kg i.v.
		4600 mg/kg orally
		6180 mg/kg s.c.
Rat	56	16.4 mg/kg i.v.
		3050 mg/kg orally
		9200 mg/kg s.c.

	Reference	Daily dose and route	Duration (days)	Toxic effects
Chronic toxicity				
Rat	30	2.2 mg/kg i.p.	35	−
		6.6 mg/kg i.p.		+
		20 mg/kg i.p.		+
		60 mg/kg i.p.		+
Dog	55	0.1 mg/kg i.v.	30	−
		0.5 mg/kg i.v.		+
		2.5 mg/kg i.v.		+
		12.5 mg/kg i.v.		+
Dog	43	0.5 mg/kg d.i.v.	30	−
		3.5 mg/kg d.i.v.		+
		24.5 mg/kg d.i.v.		+
Dog	66	0.125 mg/kg i.v.	180	−
		1.25 mg/kg i.v.		+
		7.0 mg/kg i.v.		+

(F.VII), is important in the formation of such microthrombi. Although the mechanism by which TF triggers intravascular coagulation depends on the underlying disorder, tissue injury and endothelial injury appear to be the major mechanisms involved (Fig. 3). In tissue injury such as obstetrical complications or cases of multiple trauma, the release of tissue factor into the circulation activates intravascular coagulation. Mucin and a protease produced by isolated tumor cells can activate coagulation in the absence of F.VII, that suggests that they may influence the development of DIC in cancer patients (23).

Endothelial injury is induced mainly by such cytokines as TNFα or interleukin-1β (IL1β) or by the inflammatory mediators that are derived from activated leukocytes such as granulocyte proteases or oxygen free radicals (25). Following stimulation by endotoxin or cytokines, monocytes or endothelial cells can elaborate TF at the cell surface. Endotoxin and the cytokines further decrease the anticoagulant potential of the endothelial cells by reducing the content of thrombomodulin and glycosaminoglycans, which are anticoagulant systems that operate on the surface of the endothelial cell (18). Cytokines strongly promote the expression of endothelial leukocyte adhesion molecules such as P-selectin, E-selectin, and ICAM-1 by which the activated leukocytes can adhere to the endothelial cells (9). The close contact between the activated leukocytes and the endothelial cells serves to exclude plasma components such as α_1-proteinase inhibitor (α_1PI) from this compartment (8). Thus, cytokines can contribute to the formation of fibrin in DIC associated with infection by indirectly increasing the damage induced by activated leukocytes. Leukocytes are important in the intravascular formation of fibrin induced by endotoxin in

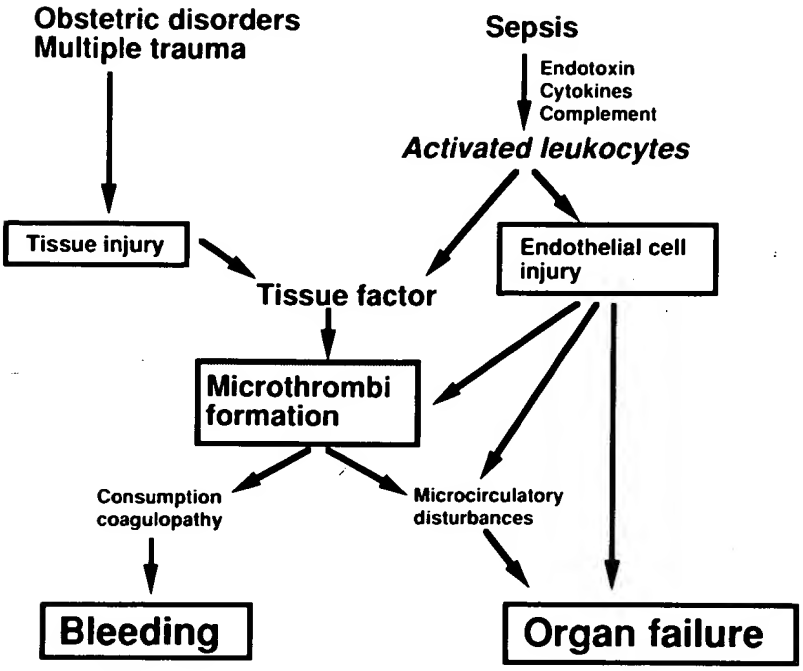

FIG. 3. Pathophysiology of disseminated intravascular coagulation.

rabbits (i.e., the generalized Shwartzman reaction) (27) and in patients with septicemia (48).

In the pathologic conditions of DIC, the leukocytes, especially the neutrophils, can be activated by microcirculatory disturbances (62), cytokines (13), F.XIIa (73), kallikrein (58), and C5a (46). Activated leukocytes then release various inflammatory mediators that damage the adjacent endothelial cells. Activated neutrophils are thus likely to be involved in the organ dysfunction of patients with DIC, especially those patients with sepsis. Consistent with this notion is the finding that neutrophil activation contributes to the respiratory failure and death of patients with DIC and serious infection (Fig. 4) (47). Granulocyte proteases and hydrogen peroxide synergistically damage the endothelial cell membranes and detach the endothelial cells from the matrix (71). These mediators also synergistically inactivate the thrombomodulin of endothelial cells in vitro, suggesting that the activation of neutrophils may exacerbate both the coagulation abnormalities and the damage to endothelial cells (1). The endothelial cell damage induced by cytokines and activated leukocytes then exacerbates the organ dysfunction due to the microcirculatory disturbance resulting from microthrombi formation. Thus, the endothelial injury induced by activated leukocytes plays a key role in the pathogenesis of DIC, particularly that associated with septicemia.

Intravascular coagulation can thus be triggered by the TF derived from the injured tissues in patients with obstetric disorders and patients with multiple trauma, or by the TF produced by the monocytes or endothelial cells following their activation by endotoxin or cytokines in patients with sepsis. In sepsis, endothelial injury produced by activated leukocytes may also exacerbate organ failure.

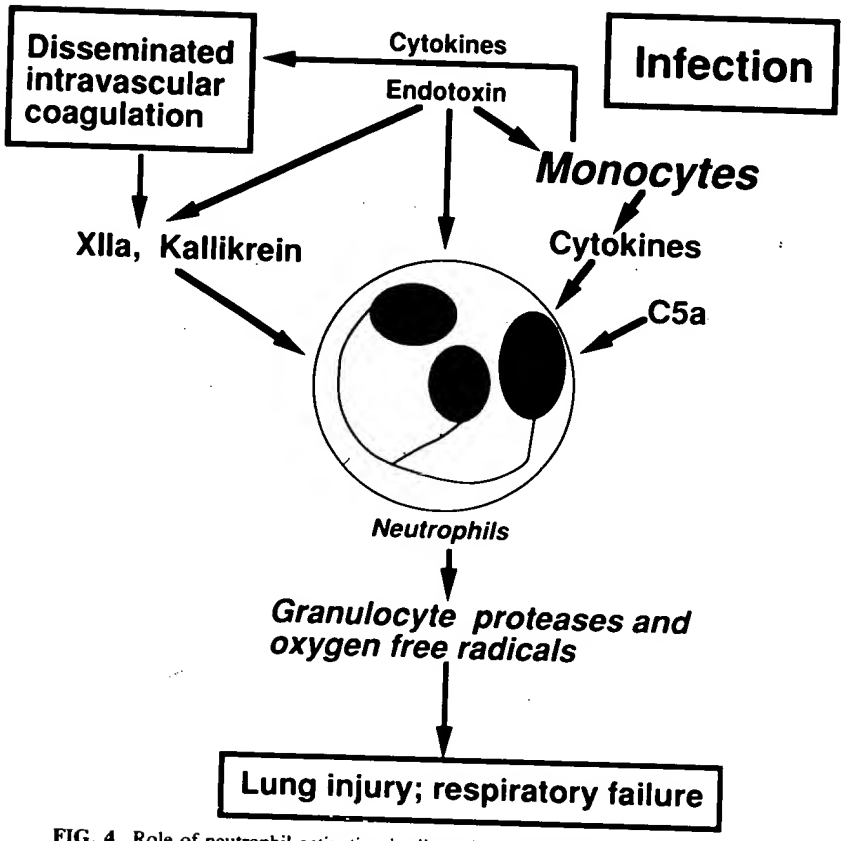

FIG. 4. Role of neutrophil activation in disseminated intravascular coagulation.

Efficacy of NM in Experimental DIC

In rats with DIC produced by the continuous intravenous infusion of endotoxin (100 mg/kg) for 4 hr, NM administered by continuous intravenous infusion (0.01 or 0.1 mg/kg) for 4 hr significantly improved the coagulation abnormalities and lessened the glomerular deposition of fibrin (79). The coagulation abnormalities induced by circulatory arrest in dogs were also ameliorated by NM, which was more effective than heparin (64).

Pulmonary Vascular Injury

Pulmonary vascular injury is often associated with DIC; the resulting respiratory failure can influence the outcome of patients with severe infection and DIC, since it may precede the onset of the adult respiratory distress syndrome (ARDS) (6).

We examined the effect of NM on endotoxin-induced pulmonary vascular injury in rats (manuscript in preparation) and found that the intraperitoneal injection of NM (1.0 mg/kg) significantly reduced the pulmonary vascular injury induced by endotoxin. Such injury was not affected by the administration of dansyl Glu-Gly-Arg-chlormethyl ketone-treated factor Xa, which is a selective inhibitor of thrombin generation, or by heparin. The

vascular injury induced in rats by endotoxin administration is significantly reduced in animals with leukocytopenia and in those administered a granulocyte elastase inhibitor (69,70). It thus seems possible that the endotoxin-induced pulmonary vascular injury is mediated by activated leukocytes, not by thrombin. NM may thus reduce endotoxin-induced vascular injury by inhibiting activated leukocytes. Its efficacy can be explained by an inhibitory effect on the complement system, F.XIIa, and kallikrein, all of which activate the leukocytes. In addition, the inhibition by NM of leukocyte aggregation or of the production of superoxide by activated leukocytes, may contribute to its efficacy.

Kuratani et al. (36) demonstrated that activated leukocytes and C5a were involved in the injury to rabbit lung produced during the reperfusion that followed cardiopulmonary bypass. Such injuries were significantly reduced by the infusion of NM. Kreil et al. (35) also showed that NM reduced pulmonary hypertension by inhibiting the release of thromboxane and the activation of complement induced by the heparin–protamine reaction.

The anticoagulant effects of NM thus prevent the intravascular coagulation induced by endotoxin, while its anticomplement properties reduce injury to the endothelial cells.

Liver Injury

Liver dysfunction is common in sepsis. The intraperitoneal injection of NM (5 mg/kg) significantly reduced the endotoxin-induced aggravation of hepatic damage in C57BL/6 mice with experimental autoimmune hepatitis (45). NM also improves the anaerobic shift of hepatic glycolysis in septic rats, probably due to its anticomplement activity (16). Accordingly, NM may prevent the liver injury associated with sepsis in humans.

CLINICAL USE OF NM IN TREATING DIC

Clinical trials to evaluate the therapeutic efficacy of NM in patients with DIC have been performed in Japan (59,63). A well-controlled multicenter study designed to evaluate the efficacy and safety of NM in DIC as compared with heparin was performed at 57 hospitals (59). Efficacy was evaluated according to the improvement in clinical manifestations and in hemostatic parameters that was observed in 56.7% of the patients with DIC who were administered a continuous infusion of NM (0.2 mg/kg/hr). This was compared with an efficacy of 47.4% in such patients administered heparin, 10 U/kg/hr intravenously. Although the overall efficacy of NM did not differ significantly from that of heparin, significantly higher efficacy rates were obtained with NM in nonleukemic patient vs. those with other malignant tumors (85.7% vs. 30.0%, $p < 0.05$ by U-test) (59). These patients developed bleeding complications on heparin, while none did so on NM. The authors concluded that NM might be an effective alternative to heparin for treating DIC. By a continuous infusion, NM (0.1 mg/kg/hr) was effective in treating 75% of patients with DIC (63). At a dose of 0.2 mg/kg/hr NM was effective in treating 70% of the patients. NM was thus as useful as heparin in treating patients with DIC.

POSSIBLE THERAPEUTIC BENEFIT OF NM IN DIC

Activated leukocytes and the systemic formation of microthrombi may be involved in the development of organ failure in DIC in the presence of sepsis. Since the extrinsic pathway is more important to fibrin formation than is the intrinsic pathway, the role of TF

is critical in the formation of microthrombi. Thus, the inhibition of TF-F.VIIa by NM may be useful in treating the coagulation abnormalities seen in patients with DIC. The IC_{50} of NM is 1.5×10^{-7} *M* for the TF-F.VIIa complex; this concentration is within the range of plasma concentrations of NM (2.8×10^{-8}–2.4×10^{-7} *M*) observed after its administration at therapeutic doses of 0.1–0.2 mg/kg/hr to patients with DIC (5).

Physiological inhibitors of the extrinsic pathway include tissue factor pathway inhibitor (TFPI) (53) and antithrombin III (AT III)-heparin (52). TFPI potently inhibits the TF-F.VIIa complex at physiological concentration in the presence of F.Xa (53) and inhibits the TF-F.VIIa complex at higher concentrations in the absence of Xa (7). Despite the apparent importance of TFPI in regulating blood coagulation *in vitro*, its role in DIC is unknown. TFPI levels are not decreased in patients with DIC (44). Administration of TFPI at a level 20-fold its normal level in serum prevents the coagulopathic response and the lethal effect of *E. coli* injection in the baboon (10). Since TFPI inhibits TF-F.VIIa only in the presence of F.Xa at a physiological concentration (7), the delay in the inhibition of TF-F.VIIa before the sufficient generation of F.Xa may explain why TFPI does not prevent the DIC induced by TF (74). Since NM inhibits TF-F.VIIa in the absence of F.Xa, it may inhibit TF-F.VIIa without delay in the initiation of DIC. Consistent with this notion is the finding that NM significantly attenuated the endotoxin-induced coagulopathic response in rats (79).

Although AT III does not inhibit F.VIIa in the absence of heparin, it does inhibit the TF-F.VIIa complex either in the presence of heparin ($Ki = 4.4 \times 10^{-7}$ *M*) (37) or on the surface of the endothelial cell where the glycosaminoglycans (GAGs) are abundant (7). However, the plasma levels of AT III are markedly decreased in DIC associated with septicemia (38). Endothelial cell surface GAGs are decreased by the action of endotoxin or cytokines (33). NM may therefore be more useful in treating patients with DIC than heparin or other synthetic protease inhibitors.

As described above, activated leukocytes may be involved in the lung injury seen in septicemia, thus leading to ARDS (6). Activation of the alternative pathway of complement system by endotoxin generates C5a, which can then activate the leukocytes in septicemia (22). In addition, the F.XIIa and kallikrein generated during the activation of the intrinsic pathway of coagulation can activate the leukocytes or the complement system (24), although these factors may not directly cause fibrin formations (Fig. 4). Since NM is a potent inhibitor of the complement system, i.e., F.XIIa and kallikrein, this agent may reduce the lung injury in patients with septicemia induced by activated leukocytes. Consistent with this notion is the observation that NM reduces the activated leukocyte-induced lung injury in an animal model of sepsis (manuscript in preparation). Thus the protective effect of NM against such organ failure induced by activated leukocytes may contribute to its efficacy in treating DIC associated with septicemia.

AT III has also been shown to be useful in treating animal models of sepsis and patients with septicemia (17,72). Emerson (17) reviewed the efficacy of AT III in animal models receiving *E. coli* or endotoxin. Prophylactic administration of high doses of AT III ameliorated DIC and improved the survival rate in animal models of sepsis. Although neither agent prevented the pulmonary vascular injury in sheep that were receiving endotoxin, the combined administration of AT III and α_1-antitrypsin significantly lessened the pulmonary vascular injury. Thus both granulocyte elastase and coagulation abnormalities may be involved in the pathogenesis of the endotoxin-induced vascular injury.

Since the granulocyte elastase and the oxygen free radicals generated by the activated leukocytes each inactivate AT III (31), inhibition of these activated leukocytes may be important for the success of AT III in treating sepsis. Since NM inhibits kallikrein, F.XIIa, and the generation of C5a which can activate the neutrophils, NM may be useful in preventing the activated leukocyte-induced inactivation of AT III. Combined administration of NM and AT III may be useful in treating sepsis, as NM may protect the exogenously administered AT III, as well as the endogenous substance against inactivation by activated leukocytes.

ACUTE PANCREATITIS

Although the etiology and pathogenesis of acute pancreatitis are poorly understood, trypsin may play a key role. Since NM is a potent inhibitor of trypsin activity, it may be useful in treating acute pancreatitis. This agent reportedly reduces the mortality rate of rabbits and rats with acute hemorrhagic pancreatitis induced by injecting trypsin or a mixture of enterokinase and sodium taurocholate into the common bile duct (14). NM significantly reduced the histological abnormalities observed in a cerulein-induced model of acute pancreatitis in rats. It reduced the size and extent of the vacuolization of the acinar cells and the severity of intestinal edema (75). Satake et al. (54) demonstrated that NM improves the coagulation abnormalities observed during experimental acute pancreatitis in dogs induced by the intraductal injection of a mixture of autologous bile and trypsin. NM also reduced the mortality rate of dogs with acute pancreatitis induced by the retrograde injection of a mixture of bile and trypsin into the pancreatic duct (54). This efficacy of NM could be partially explained by an improvement in such hemodynamic parameters as cardiac output, mean arterial pressure, and left ventricular stroke volume (15). Thus, NM prevents the inflammation of the pancreas caused by trypsin and may inhibit the potentially catastrophic events produced by the activation of the coagulation and complement systems.

The effects of NM in treating acute pancreatitis have been evaluated in clinical trials. In 13 such patients (50), NM, 10 mg infused intravenously over 2 hr, twice daily for 7 days, rapidly and substantially decreased the serum levels of amylase. There was a marked improvement in abdominal tenderness, signs of peritoneal irritation, diminished bowel sounds, and hydrothorax in 12 of the 13 patients. Clinical improvement was confirmed by ultrasound examinations and/or by CT scans.

PLASMAPHERESIS AND HEMODIALYSIS

NM, a short-acting multienzyme inhibitor of the coagulation system, may be useful in treating patients who are undergoing plasmapheresis, hemodialysis, or plasma exchange (3). This agent has a short half life of only 8 min in humans (5), so that its anticoagulant effect disappears rapidly. Thus, NM is useful in treating patients with a bleeding tendency. No clot formation was observed in the extracorporeal circuit, and no hemorrhage occurred during plasmapheresis, when this agent was used as an anticoagulant in treating patients with hepatic failure or with active bleeding foci (28,32).

NM is a useful regional anticoagulant for patients who are receiving hemodialysis (HD). In 12 patients with a high risk of bleeding during or after HD, no bleeding was observed following the continuous infusion of NM at 20–40 mg/hr for 33 sessions (3). To compare the efficacy of NM and heparin, randomized trials were conducted in 264

patients with hemorrhagic complications (2). No significant difference was observed in extracorporeal blood clotting between NM and heparin after HD. The activated partial thromboplastin times of the intracorporeal circulating blood were not significantly prolonged in the patients administered NM, whereas they are prolonged by heparin.

NM thus appears to be a more useful anticoagulant in plasmapheresis or HD than is heparin, particularly for patients with an increased risk of bleeding. NM has also been used successfully as an anticoagulant in patients undergoing open heart surgery (39) or cardiopulmonary bypass (57).

CEREBRAL VASOSPASM

NM prevents arterial narrowing in a rabbit model of experimental subarachnoid hemorrhage (SAH) (76). Its vasodilatory effect was observed even when NM was first given after 2 days of bleeding when the vasoconstriction had already peaked. NM is thought to suppress the initial, protease-dependent inflammatory response in the vessel wall. In a study of 45 patients with subarachnoid hemorrhage, 22 patients received NM soon after an operation to "clip" the aneurysm, while 23 control patients received clipping without NM. The incidence of vasospasm and the delayed ischemic neurological deficits were significantly decreased on NM vs. control (77). Results of this small pilot study need to be confirmed in a trial using randomized controls and blind assessment.

ADVERSE EFFECTS OF NM

Adverse effects associated with the administration of NM were observed in 18 (7.0%) of 257 patients with DIC (11). They included vasculitis accompanied by rash, soreness, or swelling of skin at the injection site (2.72%), hyperkalemia (1.95%), rash (1.17%), nausea and vomiting (0.78%), hyponatremia (0.39%), renal tubular acidosis (0.39%), and elevation of serum creatinine (0.39%).

Hyperkalemia observed in patients administered a continuous infusion of NM was due to the reduced urinary excretion of K^+ (49). NM and its metabolites, p-guanidinobenzoic acid and 6-amino-2-naphthol, may act on the apical membrane of the renal collecting duct cells and inhibit secretion of K^+ (40). The intermittent administration of NM may prevent such hyperkalemia. This beneficial effect may occur via prevention of the accumulation of NM and its metabolites on the luminal side of the renal collecting duct (78).

SUMMARY

Nafamostat mesilate (NM), is a synthetic protease inhibitor, inhibits serine proteases such as F.VIIa, F.XIIa, kallikrein, thrombin, components of the complement system and trypsin. NM prevents not only coagulation abnormalities, but also organ failure induced by complement-activated leukocytes in animal models of disseminated intravascular coagulation. NM has been used in treating acute pancreatitis because of its inhibitory effect on trypsin and other proteases that produce inflammation and alter hemodynamics. NM has been used effectively and safely as an anticoagulant in patients receiving hemodialysis or plasmapheresis and in those subjected to extracorporeal circulation. Its benefits were most apparent in patients at a high risk of bleeding. NM prevents postoperative cerebral vasospasm in patients with subarachnoid hemorrhage, perhaps by inhibiting the inflam-

matory response in the vessel wall. The hyperkalemia that is associated with continuous NM administration, and which is due to the inhibition of K^+ excretion from the renal collecting duct by NM and its metabolites, may be prevented by the intermittent administration of NM.

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